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Benzodiazepines: Uses and Abuses

SUMMARY

Anxiety is ubiquitous in our society. Although non-drug treatments should always be used, benzodiazepines are the drugs of choice when drugs are indicated. In double blind studies the benzodiazepines are superior to placebo in controlling acute anxiety and autonomic over-activity in psychosomatic disorders. They are also useful in a variety of other conditions such as the treatment or prevention of muscle spasms and pain, status epilepticus, drug withdrawal, stage 4 sleep disorders and akathisia. However, benzodiazepines have many side effects, produce tolerance, dependence and withdrawal syndromes and should be used cautiously. There is no evidence that benzodiazepines are useful in chronic anxiety. The short-acting drugs are safer with elderly patients and those with hepatic disease or hypoalbuminemia. Small amounts of prescription benzodiazepines should be used for the shortest possible period. Educational programs concerning the proper use of benzodiazepines should be increased. (Can Fam Physician 1982; 28:1630-1639).

SOMMAIRE

L'anxiété est omniprésente dans notre société. Bien qu'on devrait toujours faire usage de thérapies non-médicamenteuses, les benzodiazépines sont des médicaments de choix lorsqu'une médication est indiquée. Dans des études à double insu, les benzodiazépines sont supérieures aux placebo pour contrôler l'anxiété aiguë et la suractivité dans les désordres psychosomatiques. Elles sont aussi utiles pour une variété d'autres états tels que le traitement ou la prévention des spasmes et douleurs musculaires, le status epilepticus, le syndrome de sevrage médicamenteux, les désordres du sommeil de stade 4 et l'akathisie. Toutefois, les benzodiazépines comportent de nombreux effets secondaires, occasionnent les syndromes de tolérance, de dépendance et de retrait et on devrait en faire un usage prudent. Il n'y a pas d'évidence que les benzodiazépines soient utiles dans le traitement de l'anxiété chronique. Les médicaments à courte durée d'action sont plus sûrs pour les personnes âgées et celles souffrant de maladie hépatique ou d'hypoalbuminémie. Des prescriptions de petites quantités de benzodiazépines devraient être faites pour une période la plus courte possible. On devrait augmenter le nombre de programmes éducationnels concernant l'usage approprié des benzodiazépines.

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THE EFFICACY and ethics of using minor tranquilizers are frequently debated in our society. Two opposite points of view emerge. The 'conservative-stoic' view is that anxiety is normal and must be coped with; the person who resorts to using benzodiazepines is weak in character and the use of such pills will decrease his willpower, motivation and problem-solving abilities.[1, 2] This viewpoint blames the overuse of these drugs on the physician for over-prescribing, the patient for being too demanding and the pharmaceutical industry for excessive advertising.[3, 4]

In the 'liberal' view, a person in this highly complex, technological, anxiety-provoking society has the right to use any available methods to cope with his individual stresses.[3] The benzodiazepines are the least of several evils—they are less dangerous than incapacitating anxiety, alcoholism or other addictions.

These two extreme views ignore a

rational approach based on knowing who takes benzodiazepines and why, for what conditions, with what efficacy and with what dangers. It is important to know how these drugs work, what alternative coping mechanisms and treatments are available and how the decision to use medication is reached.

Extent of Use

Over 10% of adult Canadians and Americans take benzodiazepines by prescription in any one year.[5] This is similar to rates in Europe, although France and Belgium have even higher rates.[3] The use of minor tranquilizers is more common than the total use of all other psychotropic medications, including antidepressants and antipsychotics. Diazepam is probably the most commonly used drug in the western world.

Females take these drugs twice as frequently as males (20% versus 8%).[3, 6] We do not know whether this is due to role stereotyping, the nature of the relationship between female patients and male physicians, or the biological concomitants of being female (menstrual cycle, pregnancy, childbirth, and menopause). Probably males more frequently employ other remedies for anxiety, including the use of alcohol and marijuana.

Similarly, the elderly receive a disproportionate number of prescriptions for benzodiazepines.[5, 7] They are more likely to have difficulty metabolizing the long-acting benzodiazepines and are therefore more likely to have unwanted side effects and toxicity.[2, 8, 9] They are also more likely to be taking other drugs and to suffer from complex drug regimens and interactions. Although the depressive syndromes are more prevalent in this age group, antidepressants are as underused as tranquilizers are overused.[4]

Most prescriptions for benzodiazepines are written by family physicians and internists.[3, 6] Of patients who have used a psychotherapeutic drug, 85% have never seen a psychiatrist. A national survey[3] showed that benzodiazepines were prescribed for the following diagnoses:

1. Mental disorder (anxiety, depression etc.) (37%)
2. Senility and related symptoms (17%)
3. Physical disorders (circulatory, respiratory, digestive, skin, etc.) (46%)

Patients with physical disorders are given benzodiazepines as frequently, even though the basic indications for prescribing these drugs are the prevention or alleviation of psychic and emotional distress.[6, 10]

The stereotyped image of the benzodiazepine abuser is a pill-popping, bored, middle-class, self-indulgent, young suburban housewife. In fact, benzodiazepine abusers are most frequently middle-aged housewives (working outside the home or not) from the lowest socioeconomic stratum with less than grade school education, trying to cope with many real biological, psychological and sociocultural problems.[3]

Pharmacological Action

All the benzodiazepines are similar in structure and pharmacological action. Although differences in their metabolism include absorption, distribution, degradation and excretion, these must be interpreted cautiously because of high variation in individuals' metabolism and sensitivity to the clinical effects of benzodiazepines. For instance, the dose of diazepam required for relaxation for gastroscopy may vary 22-fold.[2] Nevertheless, rational use of the benzodiazepines does require some knowledge of the various compounds' pharmacokinetics.

The benzodiazepines can be divided into two groups based on the half-lives of parent compounds and their active metabolites: the long-acting and the short-acting groups.[2, 5, 8, 11-13] (See Table 1.)

TABLE 1
Half Lives (Hours) of Benzodiazepines Marketed in Canada

Long-Acting Drugs		Short-Acting Drugs	
Clorazepate	50-100	Oxazepam	5-20
Flurazepam	40-100	Lorazepam	10-15
Diazepam	20-50	Triazolam	2- 5
Chlordiazepoxide	5-30	Temazepam	8-10
Nitrazolam	18-28	Bromazepam	10-15
Ketazolam	30-50	Alprazolam	6-20
Clonazepam	18-50		

The long-acting drugs accumulate when taken daily. They are converted in the liver to active metabolites, which also have long half-lives. There may be excessive sedation the next morning or several days later, even on a fixed dose. Oral administration of chlordiazepoxide or diazepam produces more rapid and reliable clinical effects than IM injections of the same dose. IM administration results in delayed and incomplete absorption of chlordiazepoxide and diazepam, as well as delayed appearance of their active desmethyl metabolites, because the drug crystallizes in muscles. Elderly patients and those with hepatic disease metabolize these drugs more slowly and are more likely to have side effects or toxicity. They should therefore receive only half of the usual dose. Some of the long-acting benzodiazepines (e.g., diazepam) are quickly absorbed and highly lipid soluble so that they have a rapid onset of action. They may be useful hypnotics in the short term.

Conversion of the short-acting drugs by conjugation to an inactive glucuronide is extrahepatic and is not decreased by age or liver disease.[2, 8, 12, 13] Therefore, cumulative effects during prolonged therapy are much less significant than with the long-acting drugs. If the short-acting drugs are used as daytime anxiolytics, divided doses (at least bid) are required. Maximum effects are reached within a few days and residual effects terminate quickly.

Neurotransmitters

The effects of the benzodiazepines are mediated by several distinct mechanisms.[14-16] The neurotransmitters that have been implicated include norepinephrine, serotonin, GABA and glycine. Specific benzodiazepine receptors have been identified in human brain tissue,[17] suggesting that there may be specific benzodiazepine-like molecules in the brain whose activity produces an endogenous anxiolytic effect.

Stimulation of the benzodiazepine receptors enhances the effects of GABA, the principal inhibiting neurotransmitter.[8, 14] The resulting depolarization and decreased production of norepinephrine and serotonin cause sedation and anti-anxiety effects by decreasing electrical activity in the punishment and inhibitory areas of the brain. Diazepam is also a glycine receptor stimulator; because glycine normally inhibits motor neurones, diazepam functions as a muscle relaxant.

Uses of Benzodiazepines

In animals, these drugs cause disin-

hibition, and an increase in spontaneous and exploratory activity.[8] They suppress operant avoidance behavior and restore behavior suppressed by punishment.[15, 18] They attenuate the effects of stress and frustration, and decrease aggression and hostility. In humans, the benzodiazepines appear to influence these same behaviors, reducing acute anxiety and accompanying inhibition.

In Anxiety

The benzodiazepines have a wide variety of uses[8] (see Table 2). They are more effective than barbiturates and meprobamate in controlling anxiety with less sedation and other central nervous system side effects. They are less prone to abuse and addiction, less dangerous in overdose, and cause less microsomal enzyme indiction in the liver, so that there are fewer drug interactions.

TABLE 2
Uses of Benzodiazepines

1. Neurotic anxiety
2. Agitated depression
3. Side effects from antidepressants and neuroleptics
4. Hallucinogenic psychosis
5. Neuromuscular diseases
6. Seizures
   —status epilepticus
   —other
7. Alcohol withdrawal
8. Sleep disturbances
   —stage 4 disorders
   —? insomnia
9. Anesthesia and surgery
10. Psychosomatic disorders (with primary/secondary anxiety)

Anxiety attacks have a short duration and therefore patients will frequently have a spontaneous remission.[4] In addition, anxious patients will respond to a placebo 50% of the time.[4] Because of this, a practitioner who prescribes anxiolytics after an initial assessment may be misled by the positive response that many patients report. Nevertheless, these drugs have proven more effective than placebo in double blind trials with non-psychotic anxious patients.[8, 11]

In recurrent panic disorders, the tricyclic antidepressants are generally more useful. Acute anxiety attacks tend to be self-limiting and if the severity is mild or moderate, non-pharmacological treatments should be tried. These treatments include reassurance, ventilation, exploration of the symbolic meanings of stressors, problem solving, relaxation training, socialization, and desensitization.[19] If acute anxiety is severe or if chronic anxiety presents with marked flare-ups, then benzodiazepines may be useful for a short and strictly-enforced period of time (two to four weeks). PRN use to a daily limit may be preferable to a fixed dosage schedule when symptom severity varies.

In Depression

The depressive syndrome includes a dysphoric mood, loss of appetite and weight, loss of sleep with early morning awakening, and a diurnal variation in which a patient feels worse in the morning and better as the day progresses. The treatment of choice is an adequate trial of antidepressants, although minor tranquilizers may be useful if agitation is also present. The benzodiazepines are not useful in schizophrenic decompensations, although they are useful in the acute psychoses caused by hallucinogens. Sometimes the antidepressants cause restlessness or agitation as a side effect during the treatment of depression and, somewhat more frequently, the neuroleptics cause akathisia, which is an extrapyramidal side effect. The benzodiazepines may be useful for these symptoms.[20]

In Neuromuscular Conditions

The benzodiazepines facilitate the action of brain stem inhibitory interneurones, with less effect on the spinal cord, and this causes muscle relaxation which may be beneficial in neuromuscular conditions (see Table 3).

TABLE 3
Musculoskeletal Disorders That Benefit from Benzodiazepines

Cerebral palsy
Multiple sclerosis
Parkinsonism
Amyotrophic lateral sclerosis
Cerebral vascular accidents
Traumatic spinal cord lesions
Disc disease
Muscle strains and sprains

In Seizure Disorders

While diazepam is extremely useful in status epilepticus, it is less useful in seizure prophylaxis. Diazepam inhibits the propagation and generalization of seizure activity originating from a focus. It has a similar molecular configuration to diphenylhydantoin and may interact with similar receptor sites in the CNS.[8] Nitrazepam appears to have more antiepileptic activity and has been used prophylactically with grand-mal seizures and infantile spasms. Clonazepam[21] is used in the treatment of absence seizures refractory to ethosuximide or valproic acid, and in seizure disorders associated with myoclonus.

In Alcohol Withdrawal

Benzodiazepines are also widely used to attentuate alcohol withdrawal states, especially delirium tremens. Although they do decrease severe withdrawal complications they do not alter the subsequent drinking pattern. Alcoholics often tend to abuse these drugs and run the risk of a double addiction.

In Sleep Disorders

Benzodiazepines do decrease Stage 4 sleep and are useful in treating somnambulism, enuresis and night terrors, which are Stage 4 disorders. Their use in simple insomnia is more controversial, because tolerance to their hypnotic effect occurs quickly (less than one week).[8]

The benzodiazepines decrease REM sleep or dreaming less than other hypnotics such as barbiturates, glutethimide, methylprylon and possibly chloral hydrate.[8] The subjective unpleasantness of REM sleep and dream rebound does not occur when benzodiazepines are withdrawn, although rebound insomnia is reported. The danger of hypnotic drug dependence is less than with barbiturates.

As hypnotics, the short-acting benzodiazepines are superior to the long-acting drugs because they do not accumulate as much, thereby lessening daytime sedation, cognitive and motor impairment or toxicity. However, the short-acting benzodiazepines may increase the incidence of rebound insomnia and withdrawal symptoms. Although benzodiazepines are effective in acute situational insomnia (e.g., jet lag, grief reaction or hospitalization), they should not be routinely used, especially where reassurance, support, relaxation, and exploration of personal difficulties are likely to be effective. Severe insomnia may require investigation at a sleep laboratory.

In Anesthesia and Analgesia

The benzodiazepines have a number of applications in anesthesia, labor and surgery.[8] They are used in endoscopy and before general anesthesia or cardioversion. They increase analgesia, decrease opiate requirements and enhance subjective amnesia. The usual clinical doses given before delivery cause no important adverse effects upon the neonate. However, in high doses they have been associated with prolonged neonatal lethargy, hypotonia, hypothermia and respiratory depression. In anesthesia, surgery and labor, the short-acting drugs should be used more commonly.

In Psychosomatic Disorders

The benzodiazepines are frequently used in organic or psychosomatic disorders in which anxiety is believed to have a precitipating or exacerbating role.[13] Lasagna[6] and Ayd[22] reviewed the literature on the effects of benzodiazepines on psychosomatic illnesses. They reported that lorazepam decreased anxiety, hypertension and gastrointestinal complaints, including aerophagy, irritable colon and nervous dyspepsia. Diazepam resulted in decreased gastric secretion when patients with duodenal ulcer and dyspepsia were stimulated by pentagastrin.[6] Chlordiazepoxide resulted in less narcotic use in the first 24 hours on a coronary care unit than amobarbital. In the treatment of essential hypertension, Lasagna speculates that benzodiazepines may be more useful than phenobarbital and antihypertensive drugs, which result in significant side effects and non-compliance. In coronary artery disease, benzodiazepines may be useful in allaying anxiety and autonomic overactivity. They may decrease the incidence of arrythmias and sudden death in coronary care units.

Unwanted Effects And Hazards

Neurological effects[2, 8, 23] include depression, fatigue, drowsiness, somnolence, muscle weakness, nystagmus, and dysarthria. These effects are dose-dependent and are more likely to occur in the elderly, and in those with low serum albumen. Sedation occurs in 3% of patients (9% if the serum albumen is low, since benzodiazepines are normally bound to serum albumen). Residual daytime sedation and mild cognitive impairment are more likely to occur with the long-acting drugs.

Psychological effects occasionally occur and include sleep disturbances such as rebound insomnia[24] hypnagogic hallucinations and nightmares. Acute depression and suicidal ideation are reported. Paradoxical rage reactions may occur, particularly in those whose anger is kept in check by their anxiety, who are frustrated by their environment or who have a history of outbursts and impulsiveness.[8, 9]

With intravenous diazepam, occasional pain or phlebitis will occur at the injection site. Life-threatening adverse reactions, including respiratory depression and cardiac arrest, occur in 1.7% of patients after IV diazepam, especially if severe pulmonary or cardiovascular disease exists. IV diazepam should be given slowly (less than 2.5 mg/min.)[9] and only in settings where cardiopulmonary support systems are available.

Drug abuse and addiction have been reported. Any benzodiazepine can be abused and produce physiological addiction if large doses are taken over a long period of time. This danger is much less than with other drugs.[8] Although addiction is rare, withdrawal effects have been reported including anxiety, tremor, insomnia, nausea and vomiting. These symptoms occur three to ten days after withdrawal of long-acting benzodiazepines and within 24 hours of withdrawing short-acting drugs.[24] They are rare when short courses are given at recommended therapeutic dosage. These symptoms, whether psychological or physiological in origin, may falsely convince the patient or doctor of the need for continuing medication. Those patients motivated to discontinue the drug should be encouraged.

Successful withdrawal can be accomplished by dividing the total daily dose into four spaced administrations. This interrupts the usual pattern of drug-taking immediately before anticipated stresses. Successive reductions of 2-5 mg (in diazepam equivalents) each can be made at the administration time chosen by the patient. Each reduction may be followed by several days of mild anxiety and physiological arousal. When this settles, the patient is ready for the next reduction. Explanation of the pharmacology and physi-

ology of drug withdrawal is extremely useful and supportive.

Of overdosed patients presenting at an emergency department, 31% have taken benzodiazepines.[2] These are rarely fatal unless combined with other drugs. The benzodiazepines potentiate the sedative and lethal effects of alcohol and other CNS depressants, and this combination, if abused, may interfere with cognitive, intellectual and psychomotor functioning. Dependence on benzodiazepines is more likely to occur with alcoholics, even if their drinking pattern doesn't change.

On the other hand, caffeine or caffeine-containing beverages may counteract the effects of the benzodiazepines,[26] so that the patient continues taking a minor tranquilizer or increases the dose unnecessarily.

Benzodiazepines are not well absorbed in the presence of antacids, achlorhydria, or anticholinergic drugs. Diazepam is a highly lipid soluble agent and should not be given with mineral oil, which will prevent its absorption.

Benzodiazepines are not entirely safe during pregnancy or the postnatal period. They have been associated, if used in the first trimester, with cleft lips and palates.[25] High doses at delivery may produce the 'floppy infant' syndrome, characterized by apnea, hypotonia, poor sucking, risk of aspiration and hypothermia.[22] Diazepam and other benzodiazepines readily cross the placenta and reach higher concentrations in the fetal circulation than in maternal blood. They are also excreted in breast milk.[22]

Conclusions

Benzodiazepines are more effective and safer than barbiturates, meprobamate or alcohol. In double-blind trials they have been shown to be superior to placebo in treating acute anxiety, in controlling anxiety and sympathetic over-activity in psychosomatic disorders and in treating muscle spasms from many causes.[4, 8, 11]

However, the routine treatment of anxiety should involve other approaches before the prescription of benzodiazepines. In acute anxiety of mild or moderate severity, supportive psychotherapy, environmental manipulation or relaxation training may be preferred treatment.[19] In severe acute anxiety, benzodiazepines may be use-

ful for a short period of time—less than four weeks. In chronic anxiety of moderate or severe intensity, benzodiazepines show no superiority over placebo. Continuous use should be avoided; medication should be reserved for prn use in acute or intolerable flare-ups. Often the mere availability of medication is sufficient reassurance to make this use unnecessary. Consultation with a psychiatrist or therapist should be considered, particularly before committing any patient to continuous longterm drug use.

Benzodiazepines should be used cautiously in all age groups and should be used less frequently with increasing age. Short-acting benzodiazepines are preferable to long-acting ones in all age groups, especially the elderly. Patients over 65 should be given half the usual daily dose.[2, 5, 13] Long-acting cumulative drugs should be reserved for conditions where daytime sedation is acceptable, e.g., acute alcohol withdrawal or brief applications requiring a combination of night-time hypnotic and daytime anxiolytic given in a single bedtime dose.

Longterm use of these drugs (for more than one month) is of minimal or no pharmacological benefit and should be discouraged. A small percentage of users (10-13%) refuse to stop, decrease or change their use of benzodiazepines. Most of these patients have been using the drug for years. Having them stop these drugs may do them more harm than good.[5]

Continuing medical education programs on the use of minor tranquilizers could also be improved. Education of family physicians in a university-based hospital using audiovisual programs and feedback has been shown to improve prescription patterns; in a controlled study it was shown to be more effective than giving simple guidelines.[5] Each physician who practices within a hospital could receive a computer-generated profile of his or her prescribing pattern compared with the patterns of other physicians. Audits or rounds should be conducted to discuss the reasons for individual variations of prescribing practices.

In teaching hospitals, staff physicians should countersign orders for problem drugs and promote discussion about benzodiazepine prescribing.

Some educational feedback programs have not decreased the number of prescriptions, but changed the pre-

scribing pattern to a more desirable one, including greater use of short-acting benzodiazepines, at lower doses, for shorter periods of time.[13]

Diazepam and chlordiazepoxide should not be given by the IM route because of erratic and incomplete absorption.[2] If an IM injection is required, lorazepam is best. In the elderly, and in patients with liver disease or low serum albumen, the short-acting drugs such as lorazepam or oxazepam are preferable.

Alternate Solutions

Lastly, further study is required to learn why certain populations are such frequent recipients of benzodiazepine prescriptions. Alternative solutions are needed for women, single parents, the elderly, the poor and the uneducated, in dealing with anxiety and stresses partly caused by social factors and vocational and role conflicts. Ideally, specific interventions must be developed to replace the non-specific symptomatic relief that the benzodiazepines offer. ◉

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